

9. Claims 82-83, 85-86 and 88 stand rejected as obvious over Southern. The Examiner refers to arrays having 24 or 72 oligonucleotides. The Examiner says that these arrays have two probe sets, and any of the sequences could be considered a reference sequences. This rejection is respectfully traversed.

With respect to claim 82 and claims 83, 85 and 86 depending therefrom, the Examiner may have overlooked the claim requirement that probes in the first probe set have at least three interrogation positions respectively corresponding to each of at least three contiguous nucleotides in the reference sequence. (In the present claims an interrogation position is a variable position between otherwise identical probes.) By contrast, in Southern's array of 24 probes, there is only a single position that might be considered to be an interrogation position, that is the seventh nucleotide occupied by a T in the first column of probes and an "a" in the second column of probes. In Southern's array of 72 probes, there are two positions that might be considered to be interrogation positions, namely, the sixth nucleotide occupied by a "t" in the first column, a "C" in the second column and a "C" in the third column, and the seventh nucleotide, occupied by a "T" in the first column a "C" in the second column and an "a" in the third column. Thus, Southern does not disclose a first probe set having three contiguous interrogation positions, nor a second probe sets having identical probes to each probe in the first probe set except at the at least three contiguous interrogation positions.

Claim 88 is directed to an embodiment of the invention referred to as block tiling, described in the specification at *e.g.*, p. 37 *et seq.* Claim 88 specifies an array comprising a perfectly matched probe having a plurality of interrogation positions and at least three mismatched probes for each interrogation. Thus, at minimum, such an array has a perfectly matched probe with two interrogation positions, and at least two groups each having three mismatched probes for each of the interrogation position. In other words, the claims defines at least seven probes. Such an array is illustrated by Fig. 7 (except that Fig. 7 shows a perfectly matched probe with three interrogation positions and three groups of mismatched probes.)

Southern's arrays of 24 and 72 probes do not include any subset of seven probes conforming to the claim 88 requirements. As previously noted, the probes in the 24-probe array have only a single interrogation position. Thus, these probes do not satisfy even the first requirement for a matched probe having two interrogation positions.

The probes in the 72-probe array might be considered to have two interrogation positions at the 6 and 7th nucleotides as previously discussed. Thus, one might consider a probe occupying the central column of the table as being a matched probe with two interrogation probe. However, for the interrogation position at the 6th nucleotide, there is only one mismatched probe that is identical to the matched probe except at the interrogation position (*i.e.*, the probe in the first column in the same row as the probe in the central column). Likewise for the interrogation position at the 7th nucleotide, there is only one mismatched probe that is identical to the matched probe except at the interrogation position (*i.e.*, the probe in the third column in the same row as the probe in the central column). Thus, the 72-probe array of Southern at most defines a matched probe with two interrogation positions, and one mismatched probe for each interrogation position. By contrast, claim 88 specifies at least three probes for each interrogation position.

The 24 and 72 probe arrays are used by Southern for testing the specificity and conditions of hybridization with a view to incorporating the benefits of such teaching in the design of much larger complete arrays of probes that form the focus of the Southern reference. Once these experimental arrays have served their purpose of establishing suitable conditions, they are no longer needed. Thus, Southern provides no suggestion to modify the 24 or 72 probe arrays in a direction that approximates to the presently claimed invention.

11. Applicants provide a terminal disclaimer with respect to 08/510,521.
13. Claims 82-92 stand rejected under 35 USC 112, first paragraph on the basis that the length of the probe and reference sequence are critical or essential to the

practice of the invention, but not included in the claims. The Examiner says that applicants have not given enough information regarding the reference sequence or the length of the reference sequence and in the absence of such information one would not be able to determine the sequence or the length of the probes. The Examiner also says that target sequence depends on the reference sequence.

Applicants have added claims 93-94, which define lengths of probes. If other issues can be resolved and the Examiner persists with the comments about probe length, applicants will consider incorporating this limitation into the independent claims. However, for the reasons given below, submit that the rejection is in error on all grounds.

The rejection presents two distinct issues, which will be addressed in turn. First, the Examiner is requesting that the claims be amended to include subject matter that the Examiner says she believes is essential to practice of the claimed methods, namely, probe lengths and identity of a reference sequence. According to MPEP 2172.01 "essential elements" are those defined as such in the specification or from other statements of record. MPEP 2172.01. Here, the Examiner has not pointed to any statements in the specification nor otherwise of record that probe lengths or identity of a reference sequence are essential to the practice of the invention. As applicants pointed out in the last response, the specification says the opposite, namely that a range of different probe lengths can be used, and that virtually any reference sequence can be used. In the absence of statements in the specification or of record by applicants that probe length or identity of a reference sequence is essential to practice of the invention, the Examiner has no basis to require applicants to recite such in the claims.

The second issue presented by the Examiner is one of enablement. That is, can one practice the claimed methods without being limited to specific reference sequences or probe lengths without undue experimentation. The Examiner's case appears to be based in large part on the view that without a reference sequence one cannot determine the identity or length of probes or known what target sequence is a variant of the reference sequence. However, once one has selected a reference sequence, one has no difficulty determining any of these things. The only difference affecting enablement

between the claims as they now stand, and claims amended to recite a specific reference sequence, is that in the former situation, one practicing the claimed methods would have to select a reference sequence for himself. Because the specification teaches that virtually any sequence can be used as a reference sequence, it is not seen how the selection of a reference sequence represents any burden at all, much less an undue burden.

The Examiner's case for nonenablement also appears to rest in a part on a need for empirical experimentation to determine suitable probe lengths for a given target sequence. However, this position seems to assume that any empirical experimentation is undue experimentation rather than undertaking a Wands analysis of all the relevant factors. Such an analysis should take into account the extensive guidance provided by the specification in indicating preferred probe lengths (pp. 23-24) the teaching of the specification of means for testing different probe lengths (p. 25), the presence of multiple working examples in the specification, the mature state of the art (in that probe hybridizations were commonly performed at the priority date of the invention) and the high level of skill in the art. When these factors are taken into account, it is submitted that a skilled artisan would have no difficulty at all selecting suitable probe lengths for use in the claimed methods.

15. Claims 82-92 stand rejected under 35 USC 112, second paragraph for omitting essential elements, namely the length of probes and information concerning the reference sequence. This rejection is respectfully traversed.

In substance the rejection appears essentially identical to the 35 USC 112, first paragraph rejection discussed above. For the reasons indicated in the previous response, it is submitted that there is no statutory basis for this type of rejection under 35 USC 112, second paragraph. See MPEP 2172.01 in which the allegation that essential elements have been omitted is listed as a ground for rejection under 35 USC §112, first paragraph under the first clause of but is not listed as a ground for rejection under 35

USC 112, second paragraph under the second clause of MPEP.¹ Nevertheless, insofar as this rejection is made under 35 USC 112, second paragraph applicants submit the rejection is in error for the same reasons as discussed above.

16. Applicants attach a copy of the pending claims from co-pending 09/798,260. It is noted that the cited case is still at a preliminary stage (the filing fee has not yet been paid) and is unlikely to issue before the present case. Thus, even if the Examiner determines the claims are conflicting, it is submitted that a terminal disclaimer is not required.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 650-326-2400.

Respectfully submitted,



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¹ MPEP 2172.01 has two clauses. The first clause states that a "claim which omits matter disclosed to be essential to the invention as described in the specification or other statements of record may be rejected under 35 USC 112, first paragraph, as not enabling." The second clause states that a "claim which fails to interrelate essential elements of the invention as defined by the applicant(s) in the specification may be rejected under 35 USC 112, second paragraph."

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In re Application of: Maureen Cronin

Application No. 09/510,378

Filed: February 22, 2000

For: Arrays of Nucleic Acid probes on Biological Chips

The owner*, Affymetrix, Inc. of 100 percent interest in the instant application hereby disclaims, except as provided below, the terminal part of the statutory term of any patent granted on the instant application, which would extend beyond the expiration date of the full statutory term defined in 35 U.S.C. 154 to 156 and 173 as shortened by any terminal disclaimer filed prior to the grant of any patent granted on pending second Application Number 08/510,521, filed on August 2, 1995. The owner hereby agrees that any patent so granted on the instant application shall be enforceable only for and during such period that it and any patent granted on the second application are commonly owned. This agreement runs with any patent granted on the instant application and is binding upon the grantee, its successors or assigns.

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2. The undersigned is an attorney of record.

J. Liebeschuetz

3/07/03

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